REMARKS

Claims 1-50 were pending in this application. Claims 45-50 are canceled as drawn to non-elected Groups. Claims 6, 8, 10, 13, 16, 18-19, 28, 32-35, and 45-50 have been withdrawn from further consideration by the Examiner. Applicants expressly reserve the right to pursue protection of any or all of the subject matter of the canceled or withdrawn claims in a subsequent application. Claims 1, 9, 11, 13, 23, 37, and 40 have been amended and new claims 51-55 have been added.

Claims 13, 23, 37, and 40 are amended to correct typographical errors.

Claims 9 is amended to correct dependency due to withdrawn claims.

Claim 11 and 24 are amended for matters of clarity.

Support for the amendment of claim 1 can be found throughout the specification and at least at page 14, lines 8-11.

Support for new claims 51-55 can be found throughout the specification and in original claims 1, 3-5, 11, and 12 and at least at page 14, lines 8-11.

No new matter is introduced by these amendments. After entry of this amendment **claims 1-5, 7, 9, 11, 12, 14, 15, 17, 20-27, 29-21, 36-44, and 51-55 are pending in this application**.

Information Disclosure Statement

The Office action (page 3) alleges that the Information Disclosure Statement filed September 3, 2004, (IDS) fails to comply with 37 C.F.R. § 1.98(a)(2). The Office action contends that citation numbers 5, 8, 11, 12, 19-22, 27, 29-32, 34-37, 39, 43, 44, 47, 48, 50, 53, 60, 63, 67, 70, 76, 78, 79, 81, 83, 86, 88, 93-95, 97, 101, 104, 105, 109, 120, 128, 121, 123, and 128 submitted with the IDS are incomplete. Thus, these citations have not been considered. Applicants maintain that the above listed citations are complete and that the relevant portions of

each citation that caused them to be listed have been provided. The relevant portion of each citation is the abstract that was submitted; therefore these citations comply with 37 C.F.R. § 1.98(a)(2). Applicants request that the abstracts submitted as citations be considered and listed on the issued patent.

The Office has objected to the IDS submitted September 3, 2004, for allegedly failing to provide the relevant pages, place, and date of publication for citations 17, 18, 64, and 122. Applicants maintain that they have provided all of the material available for the four objected to citations. The four citation were taken from publicly available web sites that do not list a known date or place of publication. Applicants request that this objection be withdrawn and citations 17, 18, 64, and 122 be considered and listed on the issued patent.

Restriction Requirement

The Notice of Non-Compliant Amendment indicated that the Office required a listing of new claims 51-55 readable upon the elected species provided in the response submitted May 29, 2007 was not in compliance with M.P.E.P. § 809.02(a). Specifically the Office has objected to the phase "at least partially reading on the elected species." Applicants submit the following table, which lists the claims reading upon the elected species.

Elected Species	Claims
laser capture microdissection.	1-5,7-44, and 51-55 read on the elected species
reversed phase protein microarrray analysis	1-44 and 51-55 read on the elected species
a normal cell	1-15, 17, 18, 20-44, and 51-55 read on the elected species
same subject	1-17, 20-44, and 51-55 read on the elected species
abnormal growth	1-44 and 51-55 read on the elected species
post-translational modification	1-44 and 51-55 read on the elected species
EGFr phosphorylation and non-voltage gated calcium ion channels	1-44 and 51-55 read on the elected species
specific Cox-2 inhibitor and carboxyamidotriazole (CAI)	1-31, 36-44, and 51-55 read on the elected species
a growth factor pathway	1-44 and 51-55 read on the

Elected Species	Claims
	elected species

Applicants submit that the requirements of M.P.E.P. § 809.02(a) have been fulfilled.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-5, 7, 9, 11-12, 14-15, 17, 20-27, 29-31, and 36-44 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Specifically, the Office contends that the term "deranged cell signaling pathway" is indefinite and is not clearly defined in the specification. Solely in the interest of advancing prosecution claim 1 is amended herein to recite "an abnormal cell signaling pathway." Support for the amendment of claim 1 can be found throughout the specification at least at page 2, lines 16 and 20. Applicants request that this rejection be withdrawn.

Claim 1 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Specifically, the Office contends that the phrase "the therapeutic agents selected target two or more different members of a protein signaling" is unclear. Claim 1 is amended herein solely to satisfy the matters of clarity. Applicants request that this rejection be withdrawn.

Claim 3 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Specifically, the Office contends that there is no antecedent basis for the term "the subject" in line 3. Applicants traverse this rejection. Claim 3 is reproduced below and recites:

> The method of claim 1, wherein the diseased cell is obtained from tissue of **a subject**, the method further comprising isolating the diseased cell from the tissue of **the subject.** [emphasis added]

The phrase "a subject" on line 2, provides antecedent basis to "the subject" in line 3. Applicants request that this rejection be withdrawn.

Claim 24 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Specifically the Office contends that the phrase "prior success" is unclear.

Applicants have clarified the term by amending the claim to state that the combination is selected based in prior success in reducing the difference in the detected activity states in a subject from which the diseased cell was obtained. This language more clearly indicates that the combination is selected because it worked in a similar situation. Applicants submit that the phase "prior success" in the amended claim is now clear and definite in the context of claim 24 and request that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 102

Claims 1, 2, 7, 14-15, 20-23, 36-39, and 41-42 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,316,462 ("Bishop *et al.*"). Applicants traverse this rejection. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference," M.P.E.P § 2131 and references cited therein. Multiple elements of independent claim 1 as amended are not taught by Bishop *et al.* and therefore there is no anticipation.

Claims 1, 2, 7, 14-15, 20-23, 36-39, 41-42

Claim 1 recites the method step of "measuring activity states for a plurality of different signaling proteins extracted from a diseased cell." The current application defines a "diseased cell" at page 8, lines 13-25 as "a cell that is identifiable … as being involved in a pathological condition of a tissue." Bishop *et al.* is devoid of any teaching of such a diseased cell. The cells described throughout Bishop *et al.* are transformed Rat1 and Rat2 fibroblasts obtained by the genetic manipulation of the fibroblast through the insertion of an oncogene expressed from an exogenous plasmid. These fibroblasts derived from rats are not involved in a pathological condition nor are they diseased cells associated with a tissue. Therefore, these fibroblasts are not diseased cells as recited in claim 1 and as defined by the current application. Bishop *et al.* cannot teach measuring activity states for a plurality of different signaling proteins extracted from a "diseased cell" for the simple fact that Bishop *et al.* does not teach a "diseased cell."

Claim 1 has been amended to recite the method step of "measuring activity states for a plurality of different signaling proteins extracted from a reference cell." Bishop *et al.* does not teach the extraction of signaling proteins from a reference cell and therefore cannot teach the measurement of the activity states of such signaling proteins.

Claim 1 also includes the method step of "determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for corresponding signaling proteins from a reference cell." This claimed method step is not present in Bishop *et al.*, and thus there is no anticipation of claim 1. Bishop *et al.* does not teach the method step of determining a difference between "the activity states measured for the plurality of signaling proteins extracted from the diseased cell" and "the activity states measured for corresponding signaling proteins from a reference cell." The Office action, at page 6, fourth full paragraph, merely states that "Ras transformed cells are more likely to undergo apoptosis in the presence of SCH 66336 plus PD 09859 as compared to normal cells" and that these Ras transformed cells would "inherently have a different activity state" then cells that do not undergo apoptosis. While this may or may not be true, this is not what is recited in the claim. The claim requires the active method step of determining a difference between the activity state of a plurality of **signaling proteins** from a diseased cell and a reference cell. Applicants submit that Bishop *et al.* does not teach this step and there can be no anticipation.

In addition, claim 1 recites the method step of "selecting a combination of at least two different therapeutic agents that target two or more different members of a protein signaling pathway or network comprising an individual signaling protein for which a difference in activity state was detected between the diseased cell and the reference cell, wherein the agents reduce the difference in the activity state that was detected." Consistent with the observation made in the Office action on page 6, Bishop *et al.* merely appears to select the combination based on the ability to produce apoptosis in fibroblasts. While this may be a worthy selection criteria in its own right, apoptosis is not an activity state of a signaling protein and selection based on apoptosis is not synonymous with, nor does it suggest, selecting agents based on decreasing the difference between measured activity states of a protein in a diseased cell versus a reference cell. As stated above, Bishop *et al.* does not teach determining a difference in activity state of a signaling protein nor the selection of agents that reduce this difference. In the absence of such teaching there is no anticipation.

In view of the forgoing arguments, Applicants request that the anticipation rejection of independent claim 1 and dependent claims 2, 7, 14-15, 20-23, 36-39, and 41-42 be withdrawn.

Claim 20

Claim 20 includes the feature of "administering the combination to a subject from which the diseased cell was obtained." This feature is completely absent from Bishop *et al.* Bishop *et al.* does not teach obtaining a diseased cell from a subject, and certainly cannot teach the administration of the combination to such a subject. In the absence of such a teaching there is no anticipation. Applicants request that the rejection of claim 20 be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Bishop et al. in view of Bonner et al.

Claims 1-5, 7, 9, 14, 15, 17, 20-23, 36-39, 41-42 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Bishop *et al.* in view of U.S. Patent No. 6,215,516 ("Bonner *et al.*"). Specifically, the Office action contends that it would be obvious to combine the teaching of Bishop *et al.* and Bonner *et al.* to produce the methods of claims 3-5, 9, and 17. Applicants traverse this rejection. Bishop *et al.* does not teach the method steps of extracting signaling proteins from a reference cell and determining their activation states. Bishop *et al.*, does not teach the method step of "determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for corresponding signaling proteins from a reference cell." In addition, Bishop *et al.* does not teach selecting agents that reduce this measured difference. These deficiencies are not made up by Bonner *et al.* and claims 1-5, 7, 9, 14, 15, 17, 20-23, 36-39, and 41-42 are not obvious. Bonner *et al.* does not teach the comparison of the activation states signaling proteins from diseased and reference cells. At most, Bonner *et al.* discloses comparing the amount of protein in a normal cell versus a tumor cell (see Bonner *et al.* example 1). Bonner *et al.* makes no mention of selecting a combination of therapeutic agents based on any criteria, much less the reduction of differences between activation states of proteins from diseased and reference cells. All elements of the claims are not found in the combined reference, therefore a *prima facie* case of obviousness has not been presented and Applicants request that this rejection be withdrawn.

Bishop et al. in view of Bilodeau et al.

Claims 1, 2, 7, 14, 15, 20-23, 26, 27, 29-31, 36-39, and 41-42 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Bishop *et al.* in view of U.S. Patent

Application 2002/0137755 (Bilodeau *et al.*) as evidenced by Torora *et al.*, Clinical Cancer Research 9:1566-1572 ("Torora et al"). Specifically the Office contends that the combination of Bishop *et al.* and Bilodeau *et al.* renders claims 26, 27, and 29-31 obvious. As stated above Bishop *et al.*, does not teach the method steps of extracting signaling proteins from a diseased or a reference cell and determining their activation states. Furthermore, Bishop *et al.* does not teach the method step of comparing the activation states of a plurality of signaling proteins from a diseased cell and a reference cell nor does Bishop *et al.* teach the method step of selecting a combination of therapeutic agents that reduce this difference. These deficiencies are not made up by Bilodeau *et al.* and these claims are allowable. Bilodeau *et al.* does not teach the method step of determining the activation states of a plurality of signaling proteins extracted from a diseased cell or a reference cell. Therefore, Bilodeau *et al.* cannot teach determining a difference between the activation states of signaling proteins extracted from a diseased cell and a reference cell and certainly cannot teach reducing this difference. The combination of Bishop *et al.* and Bilodeau *et al.* does not teach each and every element of claims 1, 2, 7, 14, 15, 20-23, 26, 27, 29-31, 36-39, and 41-42 and there is no *prima facie* case of obviousness. Applicants request that this rejection be withdrawn.

Bishop et al., in view of Bilodeau et al. further in view of Bonner et al.

Claim 40 has been rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Bishop *et al.* in view of Bilodeau *et al.* further in view of Bonner *et al.* The Office admits that nether Bishop *et al.* nor Bilodeau *et al.* teach repeating the steps of claim 1 as is recited in claim 40 and attempts to make up for this deficiency by citing Bonner *et al.* As already noted, Bishop *et al.* does not disclose the steps of the method recited in claim 1, because Bishop *et al.* does not disclose the comparison of the activation states of signaling proteins from diseased versus reference cells. This deficiency is not made up by either Bonner *et al.* or Bilodeau *et al.* alone or in combination and claim 40 is allowable. Applicants submit that no *prima facie* case of obviousness has been presented and request that this rejection be withdrawn.

Bishop et al. in view of Lubman et al.

Claims 1, 2, 7, 11, 12, 14, 15, 20-23, 36-39, 41, and 42 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Bishop *et al.*, in view of U.S. Patent

Application Publication 2005/0230315, (Lubman *et al.*). Specifically the Office contends that the combination of Lubman *et al.* and Bilodeau *et al.* renders claims 11 and 12 obvious.

Lubman *et al.* is not prior art to claims 11 and 12 of the current application. The current application was filed March 10, 2004. Lubman *et al.* was published October 28, 2005, which is after the filing date of the current application, and therefore applicants believe that the Office contends that Lubman *et al.* is available as prior art under U.S.C. § 102 (e). Lubman *et al.* is a Continuation in Part of U.S. Application No. 10/756,068 and claims priority to U.S. Provisional Application No. 60/439,625, filed January 13, 2003. Applicants' representative has reviewed U.S. Application No. 10/756,068 and U.S. Provisional Application No. 60/439,625 and can find no text within the specification to support the use of a reverse phase protein microarray to determine the activation states of signaling proteins. In particular Applicants' representative can find no mention of the use of antibodies to phospho-proteins in any context. This material, in particular paragraph [0010]-[0012] of Lubman *et al.* (cited in the Office action), was added at the time of filing of Lubman *et al.* and thus has an effective date of March 30, 2005. This date is almost two years after the priority date of the current application, which is March 10, 2003. Lubman *et al.* is not prior art to claims 11 and 12 and they are allowable. In view of the forgoing arguments, Applicants request that the rejection of claims 11 and 12 be withdrawn.

Bishop et al. in view of Jain et al.

Claims 1, 2, 7, 14, 15, 20-23, 25, 36-39, 41, and 42 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Bishop *et al.* in view of Jain *et al.* (2000 IEEE Transactions on Pattern Analysis and Machine Intelligence 22:4-37) (Jain *et al.*). Jain *et al.* does not make up for the deficiencies present in the primary reference and claims 1, 2, 7, 14, 15, 20-23, 25, 36-39, 41, and 42 are allowable in view of the references of record. Applicants request that this rejection be withdrawn.

Bishop et al. in view of Moller et al.

Claims 1, 2, 7, 14, 15, 20-23, 25, 36-39, and 41-44 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious in light of Bishop *et al.* in view of U.S. Patent No. 6,626,044 ("Moller *et al.*"). Moller *et al.* does not make up for the deficiencies present in Bishop *et al.* and therefore claims 1, 2, 7, 14, 15, 20-23, 25, 36-39, and 41-44 are allowable. In addition, one of

ordinary skill in the art would not be motivated to combine Bishop *et al.* and Moller *et al.* because the combination would render the methods of treatment disclosed by Bishop *et al.* inoperable. The methods disclosed by Bishop *et al.* include the use of a kinase inhibitor. A kinase inhibitor reduces phosphorylation (as evidenced by Bishop *et al.* Fig. 6). By the Office's own admission Moller *et al.* discloses phosphatase inhibitors. Phosphatase inhibitors increase phosphorylation. Thus, combining Moller *et al.* with Bishop *et al.* would have the effect of canceling out any benefit that could be had from the single references. In other words, one of skill in the art would not replace a kinase inhibitor with a phosphatase inhibitor or conversely replace a phosphatase inhibitor with a kinase inhibitor. A *prima facie* case of obviousness cannot be established where the proposed modification renders the prior art unworkable (M.P.E.P. § 2143.03 VI). No *prima facie* case of obviousness has been established with respect to claims 1, 2, 7, 14, 15, 20-23, 25, 36-39, and 41-44 and Applicants request that this rejection be withdrawn.

New Claims

Claims 51-54

New claims 51-55 include the method step of "using reverse phase protein microarray analysis of phosphorylated signaling proteins using antibodies that specifically bind to a particular phosphorylated signaling protein". This step is not taught nor suggested by the prior art and these claims are allowable.

CONCLUSION

The claimed method offers exceptional advantages over the prior art. The method effectively maps the activity states of proteins extracted from diseased cells to discover coordinated signal transduction events that can be targeted with combinations of therapeutic agents and provide surprising synergistic effects that permit treatment of signaling abnormalities with lower doses of potentially toxic agents. Because normal and diseased cells can be compared for a particular individual, the disclosed method can be used to diagnose an individual with high accuracy and select combinations of therapeutic agents that are tailored to the particular individual rather prescribing a treatment based on the statistical probabilities of a clinical trail.

It is respectfully submitted that the present claims are in a condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned prior to issuance of the next Office action in order to arrange a telephone interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution and allowance of the claims.

Respectfully submitted,

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